CHAPTER 1

Mechanisms of arrhythmias

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The mechanisms of arrhythmias can be broadly categorized into abnormalities of impulse conduction, abnormalities of impulse formation, or a combination of both (Table 1.1). Impulse conduction describes how an arrhythmia is perpetuated through the heart. Impulse formation describes how an arrhythmia is initiated.

Abnormalities of impulse conduction include reentry and conduction block; abnormalities of impulse formation include enhanced automaticity and triggered activity.

Usually, it is not possible to identify the exact mechanism of an arrhythmia during routine clinical evaluation and on a surface electrocardiogram. Advanced electrophysiological studies can however provide insight to the underlying mechanism. Importantly, one mechanism may be responsible for the initiation of an arrhythmia and another for its perpetuation. Understanding the mechanisms of arrhythmias remains a helpful tool in the management of rhythm disorders.[1–4]

THE CONCEPT OF HETEROGENEITY

The ventricular myocardium is comprised of different layers of cardiomyocytes that form a mosaic of cells with varying electrical characteristics. These include differences in action potential duration and refractoriness, which is particularly crucial during the repolarization phase. Cardiomyocytes can thus be further categorized as epicardial, mid-myocardial (or M cells), and endocardial myocytes. These differences in refractoriness contribute to the heart's inherent heterogeneity. The action potentials of M cells and epicardial myocytes both exhibit a prominent phase 1 and phase 3 due to the prevalence of an outward potassium current (I_{to}). However, this current is almost nonexistent in endocardial cells, resulting in the absence of or a discrete phase 1 of the action potential. Epicardial cells exhibit a higher I_{to} density than M cells, which gives their action potential a prominent spike and dome appearance. Conversely, M cells have a longer action potential duration, likely due to a lower I_{Ks} density that prolongs phase 2 of the action potential.[1–4]

These differences in potassium handling create a transmural gradient of repolarization across the myocardium (Fig. 1.1).[1–4] This transmural electrical heterogeneity can serve as a substrate for arrhythmogenesis, particularly in the presence of abnormal conditions such as heart failure, cardiomyopathy, ischemia, and drug therapy.

ABNORMALITIES OF IMPULSE CONDUCTION

REENTRY

Reentry occurs when an electrical impulse becomes entrapped in an abnormal circuit within the heart muscle that allows for its continuous excitation. In the normal heart, the electrical impulses from the sinus node propagate in an orderly manner within the myocardium to stimulate rhythmic contractions. However, if an area of the myocardium is in the refractory state and cannot conduct the normal electrical impulse secondary to a *unidirectional block*, it serves as a potential pathway for that initial impulse to reactivate the myocardial tissue once it has recovered excitability. A persistent re-excitation is known as a reentry and can perpetuate tachyarrhythmias.[5,6]

For a reentry circuit to form, certain prerequisites must be present:

1. An area of nonconducting tissue (anatomical vs. functional).
2. A pathway with a long refractory period where a unidirectional block occurs.
3. A pathway with slow conduction velocity where impulse conduction occurs.
4. An initiating trigger.

TABLE 1.1. Summary of arrhythmic disorders, their site of origin and mechanisms (including abnormalities in impulse formation and conduction), and clinical examples.

Disorder	Mechanism/site of origin	Clinical example
Abnormal impulse formation		
Automaticity		
Enhanced normal automaticity	Enhanced automaticity of the sinus node, atrioventricular node, or His–Purkinje fibers	■ Focal junctional tachycardia ■ Nonparoxysmal junctional tachycardia ■ Sinus tachycardia
Enhanced abnormal automaticity	Enhanced automaticity of atrial or ventricular myocardium and tributary veins	■ Focal atrial tachycardia ■ Pulmonary vein firing
Depressed automaticity	Depressed automacity of the sinus node	■ Sinus node dysfunction
Parasystole	Ectopic focus within the myocardium protected by entry block	■ Atrial parasystole ■ Ventricular parasystole
Triggered activity		
Early afterdepolarization	Phase 2 or phase 3 depolarization of the atrial myocardium, ventricular myocardium, or His–Purkinje fibers	■ Inherited ventricular arrhythmias (German Shepherd, English Springer Spaniel) ■ Torsades de pointes ■ Antiarrhythmics with proarrhythmic properties ■ Pulmonary vein firing
Delayed afterdepolarization	Phase 4 depolarization of the atrial myocardium, ventricular midmyocardium, or His–Purkinje fibers	■ Catecholaminergic polymorphic ventricular tachycardia ■ Digitalis toxicity
Abnormal impulse conduction		
Conduction block	Functional, anatomical, physiological, or pathological block within the sinus node, atrioventricular node, or His–Purkinje system	■ Sinus exit block ■ Interatrial block ■ Atrioventricular block ■ Bundle branch block
Reentry	■ Anatomical/functional ■ Phase II reentry, reflection ■ Accessory pathways ■ Ventricular myocardium ■ Atrial myocardium ■ Atrioventricular node ■ His–Purkinje fibers	■ Monomorphic ventricular tachycardia ■ Accelerated idioventricular rhythm ■ Orthodromic atrioventricular reciprocating tachycardia ■ Atrioventricular nodal reciprocating tachycardia ■ Atrial flutter ■ Atrial fibrillation

Therefore, a reentry circuit is typically comprised of two pathways, or branches, separated by an area of non-conducting tissue. These two branches can be differentiated into an α-*branch,* where antegrade conduction occurs, and a β-*branch,* where retrograde conduction takes place. Figure 1.2 describes the potential outcomes of a reentry circuit. A slow conduction velocity along the α-branch gives enough time for the β-branch to recover from a block, and the impulse conducts retrogradely up the β-branch. Once it reaches the α-branch again, the impulse may stop if the tissue is still in a refractory state or re-excite the α-branch initiating a second loop of reentry.

Initiation and maintenance of reentry depend on two critical parameters: the conduction velocity of electrical impulses along the reentrant pathways and the refractory periods of the circuit's components. These two factors dictate the reentrant wavelength, which is calculated as the conduction velocity multiplied by the refractory period.[5] For reentry to propagate, the reentrant wavelength must be equal to or shorter than the anatomical circuit available for the electrical impulse to propagate.

Reentry can be subdivided into two types: anatomical and functional. Moreover, six different models of reentry have been proposed:

1. Ring model
2. Leading circle model
3. Figure-of-eight model
4. Spiral model
5. Reflection
6. Phase II reentry

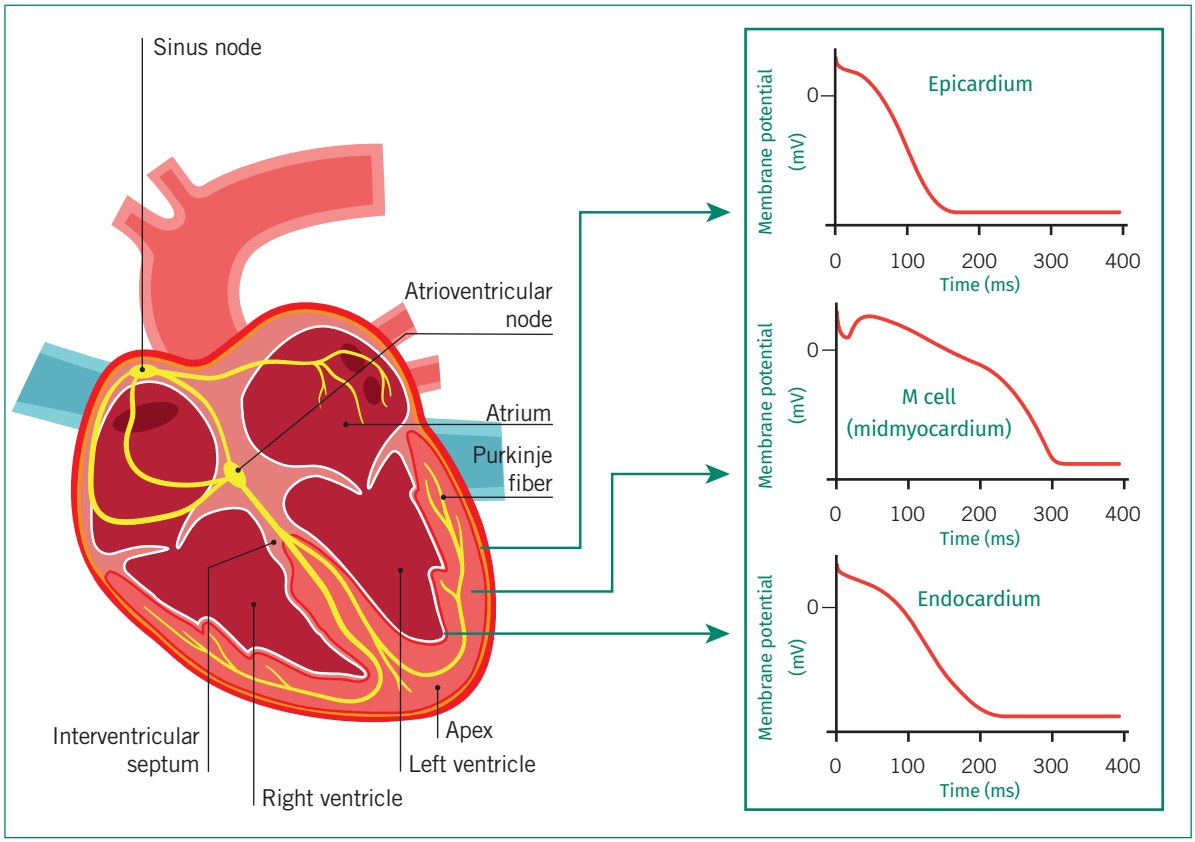

FIGURE 1.1. Concept of heterogeneity within the ventricular myocardium including the epicardium, M cells, and endocardium. Note the differences in action potential morphologies and durations, particularly during repolarization. The endocardial layer displays a slurred phase 1 due to a lower I_{to} current. M cells have longer action potentials due to a lower I_{Ks} current. The epicardial layer maintains a spike and dome appearance because of a prominent I_{to} current.

Anatomical reentry involves the presence of an anatomical obstacle around which an electrical impulse travels following a fixed path.[5,6] Examples of anatomical obstacles include the valve annulus or areas of fibrotic tissue. As the anatomical circuit is typically slightly longer than the reentrant wavelength, this type of reentry possesses an excitable gap, which is an area of excitable myocardium that exists between the head and the tail of the electrical wavefront and allows for continuous reactivation and propagation of an arrhythmia. An increase in conduction velocity along the α-branch of the circuit or an increase in the refractory period in the β-branch may prevent the reentry from occurring. Conversely, a reduction in conduction velocity or an increase in the refractory period may promote the arrhythmia (Fig. 1.3). This type of reentry is also frequently termed *circus reentry*.

Examples of anatomical reentry circuits include orthodromic atrioventricular reciprocating tachycardia, atrioventricular nodal reciprocating tachycardia, atrial flutter, and some forms of ventricular tachycardia. These arrhythmias are examples of the ring model of reentry (Fig. 1.4).

Functional reentry does not require a fixed anatomical circuit to propagate. Rather, this form of reentry involves an ever-changing central core of functionally refractory tissue and therefore depends on the refractory period of excitable tissue. The wavefront of a functional reentry circuit causes cardiomyocytes within a circuit to be immediately reactivated by the wavefront once they have recovered since the head and the tail of the wavefront nearly overlap, leaving no excitable gap. These types of pathways typically follow the leading circle, spiral, and figure-of-eight models (Fig. 1.5). Circus reentry has also been described with functional reentry circuits but is mostly associated with anatomical reentry. Examples of functional reentry include atrial fibrillation, some forms of ventricular tachycardia, and ventricular fibrillation.

Reflection typically occurs in a linear rather than circular fashion. The impulse travels linearly and parallel to an

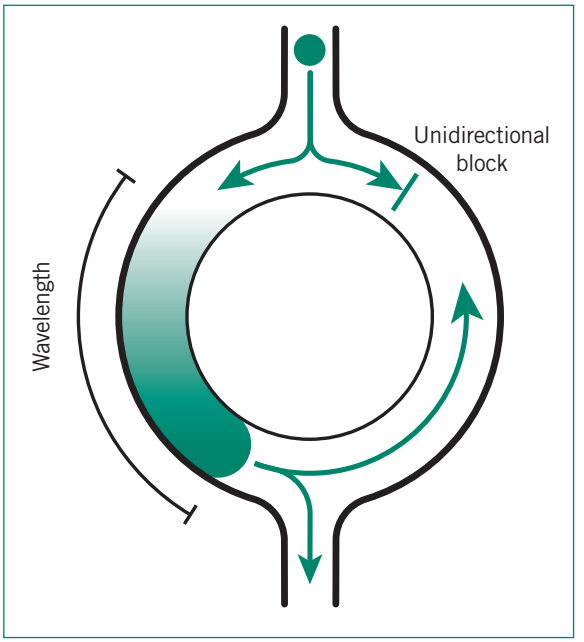

FIGURE 1.2. Schematic representation of a reentry circuit containing two branches of impulse conduction separated by an area of nonconduction.

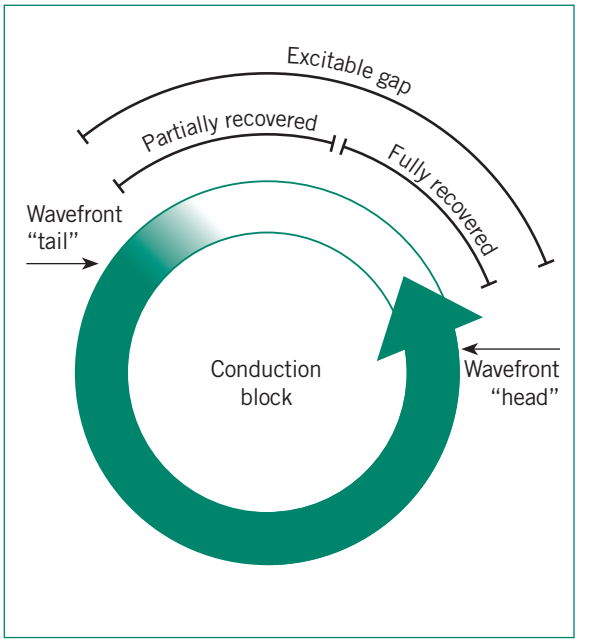

FIGURE 1.3. An excitable gap associated with an anatomical reentry circuit. Notice how the excitable gap maintains an area of fully recovered and partially recovered cells between the head and the tail of the electrical wavefront. This helps potentiate the reentry circuit.

area of depressed conduction in an antegrade direction. When the wavefront reaches the distal portion of tissue with decreased conduction, that tissue is then re-excitable, and the impulse then reverses its direction to reenter the circuit, and propagates in a retrograde direction, thereby creating a reentry loop (Fig. 1.6).

Phase 2 reentry is the development of an arrhythmia due to a change in the heterogeneity of the layers of the myocardium. Changes in refractoriness secondary to inward or outward ion currents can alter the morphology and duration of action potentials within the myocardial layers and potentially promote reentry during phase 2 (or dome phase) of the action potential. This can be observed with a decreased outward I_{to} current in the epicardium, resulting in changes in its spike and dome appearance. This is also described as the underlying cause of ventricular arrhythmias in humans with Brugada syndrome secondary to a mutation in the inward sodium channels, which has not yet been described in veterinary species.[7]

CONDUCTION DISTURBANCES

The impaired transmission of electrical impulses within the cardiac conduction system is known as a *conduction block*. These disruptions can lead to a *partial* or *complete block* of impulse conduction that can be secondary to a physiological or pathological block due to an *anatomical block* or *functional block*.

A partial block describes a decrease in the conduction velocity of a propagated impulse, while a complete block results in the abrupt termination of the conducted impulse.

A physiological block occurs due to the inherent properties of the cardiac conduction system. If an electrical wavefront is conducted with a short cycle length down a pathway that is still in its refractory state, then the impulse will not be conducted. This can result in complete block or partial block and potential aberrant conduction. These types of blocks are commonly identified with supraventricular tachycardias and result in second-degree atrioventricular block or bundle branch block; they are a mechanism that protects the ventricles from a rapid heart rate.

A pathological block occurs when there has been damage to the electrical conduction system (e.g., fibrosis, inflammation, or ischemia) that prevents impulse propagation. These can result in an anatomical block, which is caused by an anatomical lesion within the conduction system, or a functional block when an electrical impulse attempts to travel through a portion of the conduction system during its refractory state. Functional blocks can be

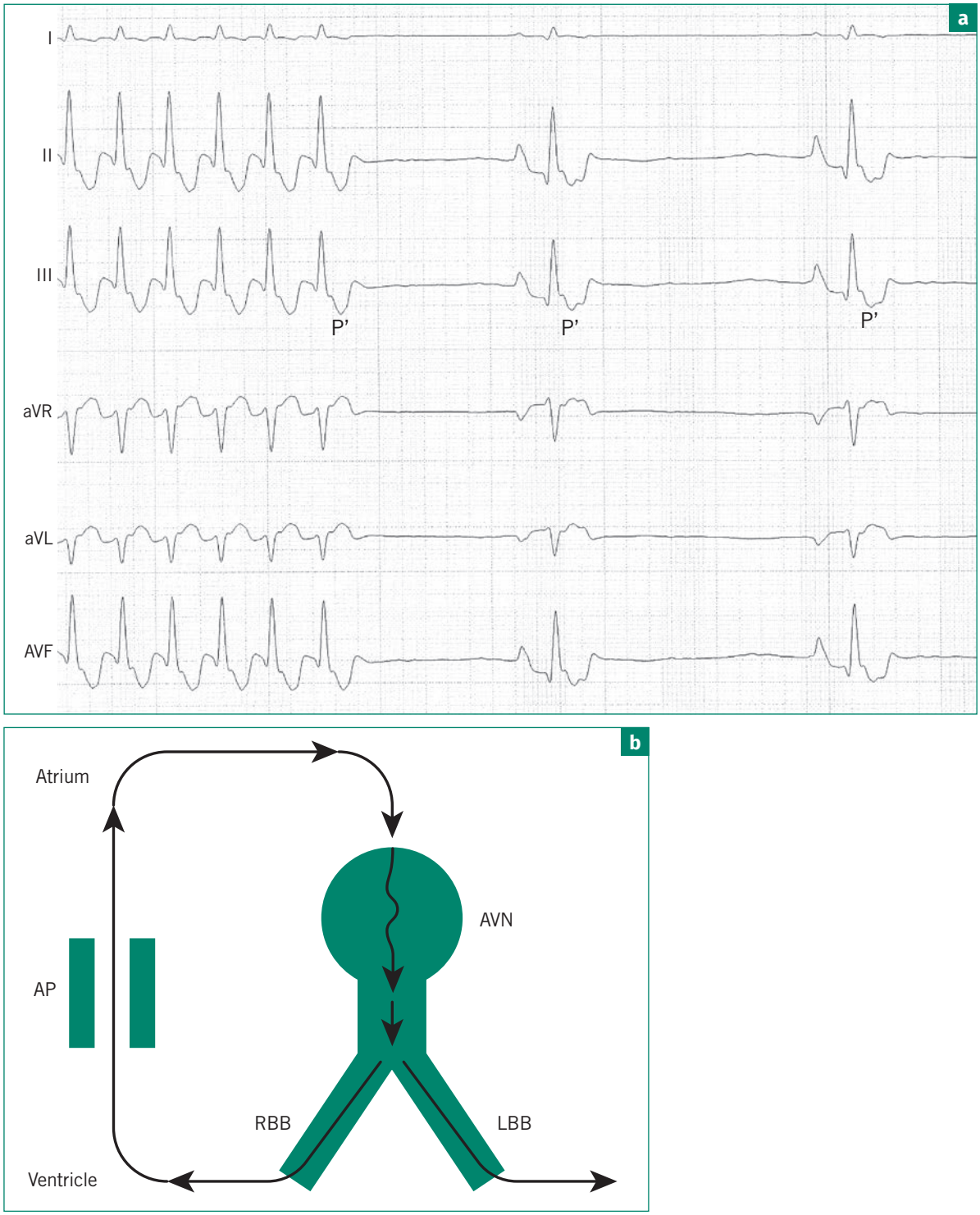

FIGURE 1.4. An example of the ring model of reentry involving the presence of an accessory pathway, responsible in this case for orthodromic atrioventricular reciprocating tachycardia. a) Six-lead electrocardiogram of a dog with an accessory pathway. During the first part of the tracing, orthodromic atrioventricular reciprocating tachycardia is present and terminates abruptly with an atrial depolarization (P') block in the atrioventricular node region. The following sinus beats conduct retrogradely as evidenced by the presence of a negative P' wave in the ST segment. b) In this circuit, impulses from the atrium conduct antegradely down the atrioventricular node, into the ventricular myocardium, and then retrogradely through the accessory pathway back into the atrial myocardium. AP, accessory pathway; AVN, atrioventricular node; LBB left bundle branch; RBB right bundle branch.

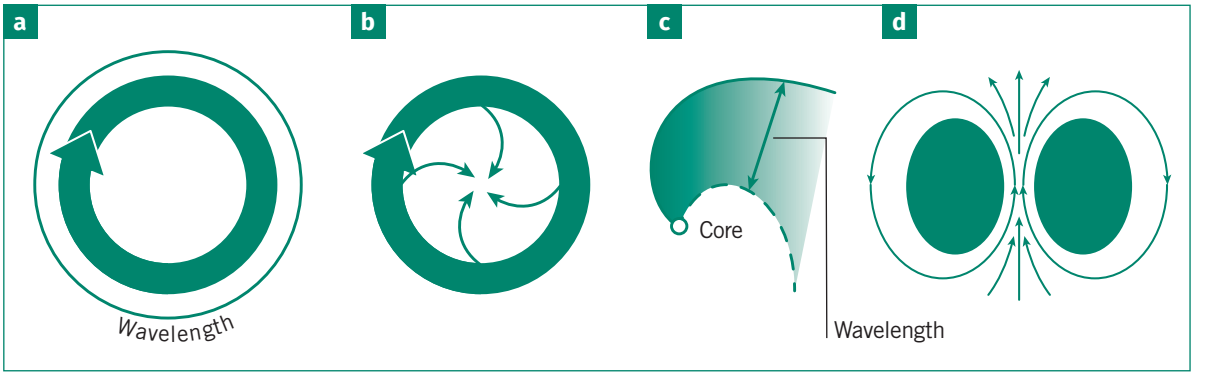

FIGURE 1.5. Examples of the different models of functional reentry. a) Schematic drawing of a functional reentry circuit. Compared to an anatomical reentry circuit, functional reentry circuits commonly do not contain an excitable gap; therefore, the head and the tail of the wavefront almost overlap, allowing for continuous reactivation and propagation of an electrical impulse. b) The leading circle model shows an electrical wavefront revolving around a core in a sustained state of refractoriness due to the constant activation of electrical impulses. There is no anatomical barrier present. c) The spiral model shows a refractory core (sometimes called a filament) around which the electrical wavefront rotates, like in the leading circle model. d) The figure-of-eight model shows two reentrant loops that travel around an area of nonconduction (green portions) and in opposite directions (counterclockwise and clockwise) but share a central portion of their circuits between the two areas of nonconduction.

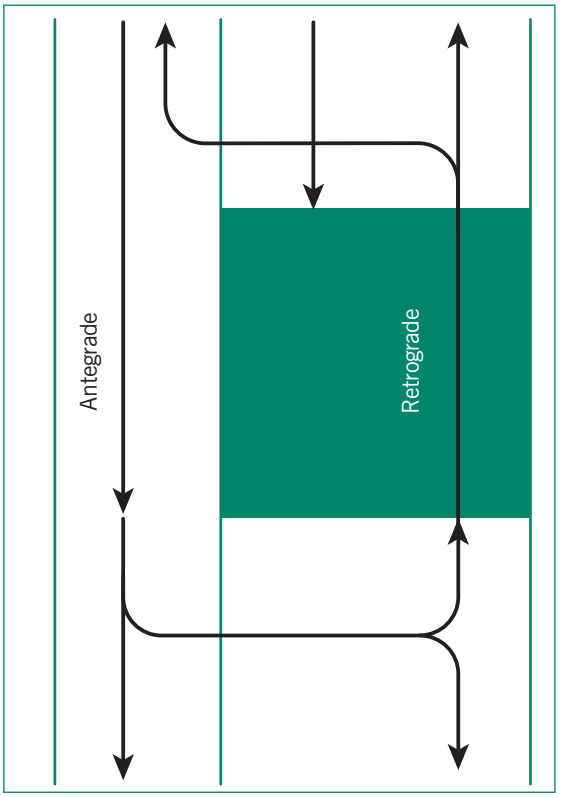

FIGURE 1.6. Reflection. In this model of reentry, a wavefront travels antegradely and parallel to an area of tissue with decreased conduction (green square). Once the wavefront reaches the distal end of the area of depressed conduction, that area is no longer refractory and becomes re-excited. The impulse then travels retrogradely within the tissue and can either be blocked at the proximal region or propagate reentry.

termed *rate-dependent blocks* as different bradyarrhythmias and tachyarrhythmias can result in blocks occurring at different phases of the action potential.

Two types of functional blocks exist (Fig. 1.7):[8]

- A *tachycardia-dependent (or phase 3) block* occurs when electrical impulses are blocked when they arrive at an area that has not yet recovered from refractoriness.
- A *bradycardia-dependent (or phase 4) block* is due to decreased excitability of cardiomyocytes during diastole.

ABNORMALITIES OF IMPULSE FORMATION

ENHANCED AUTOMATICITY

Automaticity is the ability for cardiac cells to undergo spontaneous depolarization, which results in an action potential and therefore in rhythmic contraction of the working cardiomyocytes. Automaticity is a characteristic of nodal cells due to their inherent ability to spontaneously depolarize.

The sinus node, or "dominant pacemaker", exhibits the highest intrinsic rate of automaticity. In contrast, cells of the atrioventricular node, bundle of His, and Purkinje network—known as *subsidiary pacemakers*— have lower intrinsic rates and thus typically act as latent pacemakers. Tissues with pacemaker properties can also be found in the atrial and ventricular myocardium, particularly within

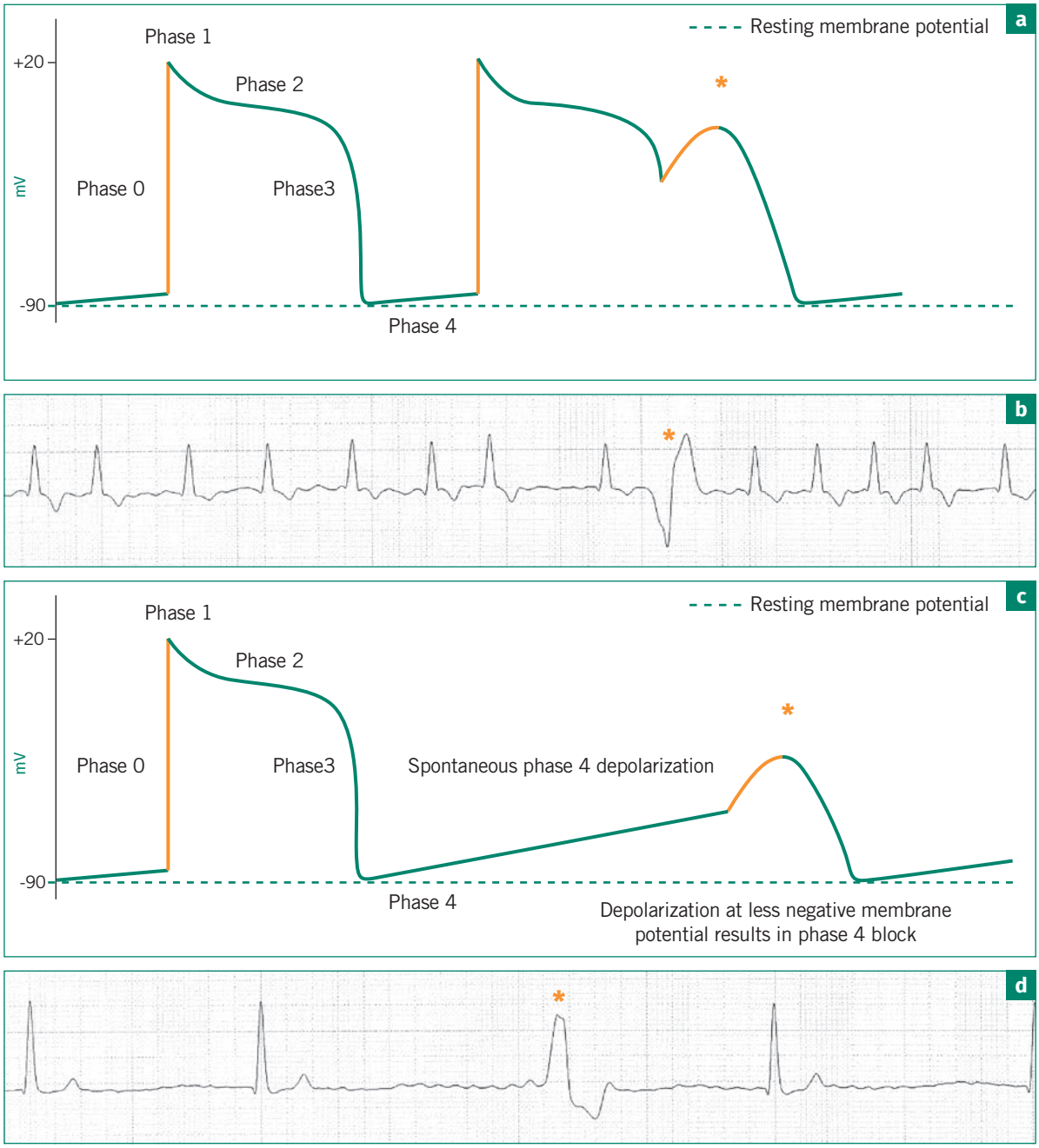

FIGURE 1.7. Rate-dependent conduction block. a) Diagrammatic representation of a phase 3 conduction block, or tachycardia-dependent block. When a stimulus occurs during phase 3 of an action potential, most sodium channels are in an inactivated state and a new action potential is not generated. b) Example of phase 3 aberrancy (rate-dependent right bundle branch block). At the organ level, a phase 3 block limited to some areas of the myocardium leads to phase 3 aberrancy. When the cycle length of an arrhythmia is shortened, or a premature beat occurs, the electrical impulse is blocked (*) in one of the bundle branches that is still in its refractory state. This is commonly associated with a right bundle branch block because the right bundle branch has a longer refractory period than the left. This is also the mechanism of Ashman's phenomenon. c) Diagrammatic representation of a phase 4 block. During periods of bradycardia or abrupt slowing of the heart rate, phase 4 of the action potential can be associated with spontaneous depolarization of the membrane potential in diseased tissues. As a result of a less negative membrane potential, fewer sodium channels are available, which can result in a conduction block when the next stimulus reaches the tissue. d) Example of phase 4 aberrancy (bradycardia-dependent aberrancy). At the organ level, a phase 3 block limited to some areas of the myocardium leads to phase 4 aberrancy (*).

the outflow tracts, tributary veins, and heart valves.[7] However, subsidiary pacemakers can discharge at a faster rate than the underlying sinus rate when the automaticity of the sinus node is depressed or their own automaticity is enhanced.

Under normal conditions, subsidiary pacemaker cells are suppressed via *overdrive suppression* from the sinus node. When these subsidiary pacemaker cells are repeatedly activated, an accumulation of intracellular sodium ions occurs, which triggers the sodium–potassium ATPase pump. This process leads to hyperpolarization, meaning the membrane becomes more negatively charged. Hyperpolarization of the subsidiary pacemaker cells prevents them from initiating an action potential before the sinus node undergoes another depolarization cycle.

The ability for nodal cells to undergo spontaneous depolarization is due to the inherent presence of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, which results in a slow influx of sodium ions, or "funny" current (I_f), and therefore in a continuous slow rise of the membrane resting potential during diastole (phase 4 of the action potential). Once the threshold is reached, an action potential occurs due to an influx of calcium through T-type and L-type calcium channels (phase 0).

The slope of phase 4 to reach the threshold is also impacted by the autonomic nervous system: heightened sympathetic tone will increase the slope of phase 4 to threshold, thus resulting in an increased discharge frequency (or faster heart rate); conversely, heightened parasympathetic tone will decrease the slope of phase 4 to threshold and result in a decreased discharge frequency (or slower heart rate). These are the characteristics of enhanced or depressed automaticity, respectively. The firing rate of pacemaker cells is influenced by the maximum diastolic potential, the action potential threshold, and the slope of phase 4 of the action potential (Fig 1.8).[3,5]

ENHANCED ABNORMAL AUTOMATICITY

Contractile cells of the heart are usually quiescent unless stimulated by nodal cells and therefore do not possess inherent properties of automaticity. However, under abnormal conditions, these cells may acquire automaticity and predispose patients to abnormal rhythms such as premature beats and tachyarrhythmias (e.g., focal atrial tachycardia and ventricular tachycardia).

These acquired mechanisms of enhanced abnormal automaticity can be explained by abnormalities in the membrane potential: a more positive resting membrane potential is closer to the threshold for action potential generation, which may cause underlying contractile cells to

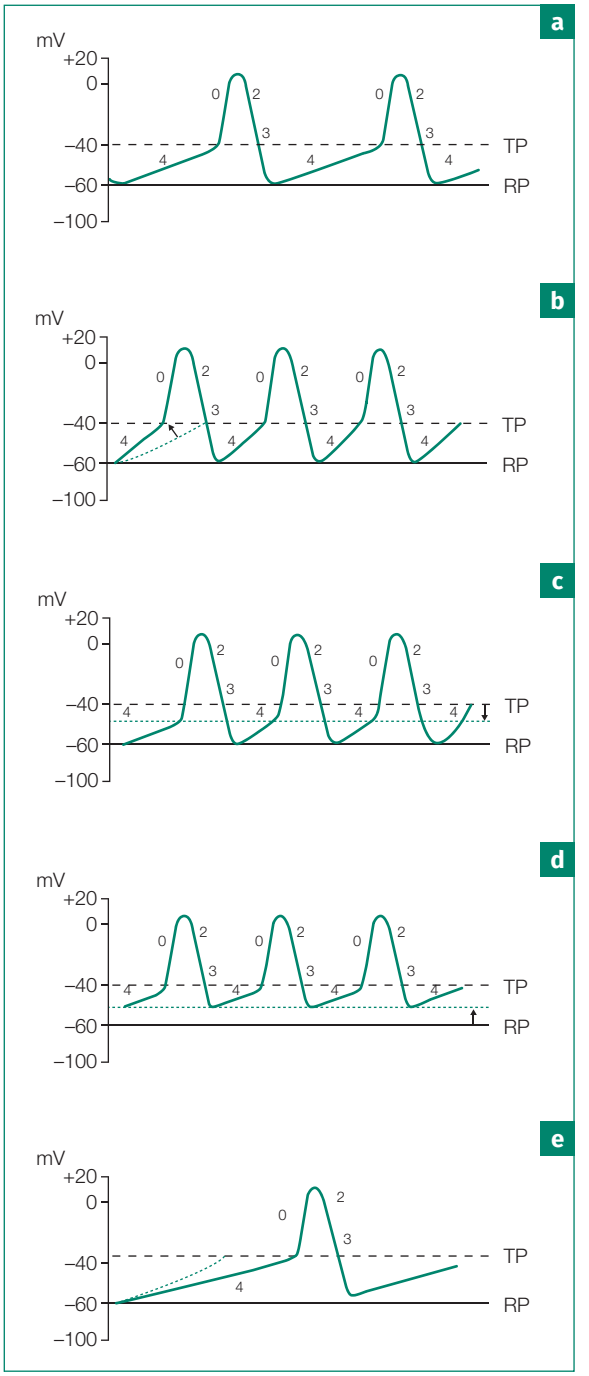

FIGURE 1.8. Concept of automaticity. Schematic representation of automaticity of the sinus node and the effects of enhanced and depressed automaticity. a) Normal sinus node firing. b) An increased slope of phase 4 results in increased frequency of discharges (faster heart rate). c), d) A more negative threshold potential (c) or a less negative resting membrane potential (d) may also result in more frequent impulse firing (faster heart rate). e) A decreased slope of phase 4 results in a decreased frequency of discharges (slower heart rate). TP, threshold potential; RP, resting potential.

become easily excitable. Causes of increased membrane potential include acidosis, hyperkalemia, and increased catecholamines. Enhanced abnormal automaticity is also more resistant to mechanisms of overdrive suppression than enhanced normal automaticity.[5]

TRIGGERED ACTIVITY

Triggered activity occurs when quiescent cells fire prematurely during an action potential due to a triggering event such as changes in autonomic tone, aberrant depolarizations, or drug effects. These triggering events result in oscillations, also known as *afterdepolarizations*, of their membrane potential after the onset of the action potential. Afterdepolarizations are categorized based on the phase during which they take place within the action potential. Whenever these oscillations reach the threshold potential, a new action potential is generated before complete repolarization of the initial action potential and results in a premature beat or a sequence of ectopic beats.

Afterdepolarizations are classified as:

1. Early afterdepolarizations (EADs)
2. Delayed afterdepolarizations (DADs)

EARLY AFTERDEPOLARIZATIONS

Early afterdepolarizations occur during phase 2 or phase 3 of the action potential and are typically associated with a prolonged action potential duration. Therefore, the ventricular mid-myocardial cells (M cells), characterized by their long action potentials, exhibit a higher inherent susceptibility to developing early afterdepolarizations. Moreover, early afterdepolarizations are more likely to occur during bradycardia, a condition associated with an increased action potential duration.

Early afterdepolarizations typically result from a reduction in the outward potassium currents, which are responsible for the repolarizing phases of the action potential. This leads to a prolongation of the action potential, thus allowing for recovery and reactivation of the L-type calcium channels and an influx of calcium. The increase in intracellular calcium then activates the sodium–calcium exchanger, which transports one calcium ion out of the cell for three sodium ions into the cell (net positive charge). This can result in a new, premature action potential if the membrane voltage crosses the threshold potential. An early afterdepolarization can occur when the membrane potential is -30 mV during phase 2 or -60 mV during phase 3 (Fig. 1.9a).[6]

Clinical situations that may promote early afterdepolarizations include heart block, acidosis, hypokalemia, hyperkalemia, and hypothermia. Some antiarrhythmic drugs may also predispose patients to early afterdepolarizations due to an effect on action potential duration, such as class Ia antiarrhythmics (quinidine and procainamide) and class III antiarrhythmics (sotalol via inhibition of the I_{Kr} current). In the German Shepherd dog, early afterdepolarizations have been described as the underlying cause of an inherited ventricular arrhythmia that typically occurs during periods of slower heart rates.[9–12] A *KCNQ1* genetic mutation causing QT prolongation in English Springer Spaniels has also been described and predisposes the breed to early afterdepolarizations and subsequent malignant arrhythmias.[13] A *QIL1* genetic mutation identified in Rhodesian Ridgebacks has also been described as predisposing the breed to ventricular arrhythmias that are likely associated with early afterdepolarizations.[14,15]

DELAYED AFTERDEPOLARIZATIONS

Delayed afterdepolarizations occur during phase 4 of the action potential because of an increased intracellular calcium concentration independent of L-type calcium channels. The increase in cytosolic calcium activates the sodium–calcium exchanger, leading to an influx of three sodium ions and an efflux of one calcium ion. This imbalance results in an intracellular net positive charge, potentially raising the membrane voltage to the threshold potential and triggering another action potential (Fig. 1.9b). Delayed afterdepolarizations are typically associated with disorders causing tachycardia.

Increased circulating catecholamines, digitalis toxicity, hypercalcemia, hypokalemia, and myocardial reperfusion can cause an increased predisposition to delayed afterdepolarizations.

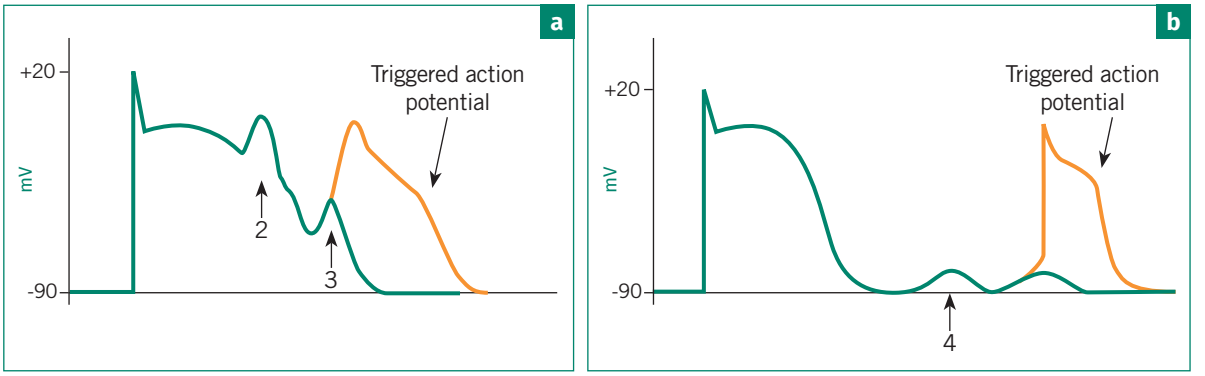

FIGURE 1.9. Triggered activity and afterdepolarizations. a) Early afterdepolarizations occurring during phase 2 (~-30 mV) or phase 3 (~-60 mV) of the action potential. If the early afterdepolarization reaches the threshold, it can generate a new action potential. b) Delayed afterdepolarizations occurring during phase 4 (~-90 mV) of the action potential. Note the shortened action potential duration, usually due to tachycardia. If oscillations (or afterdepolarizations) exceed the threshold, then a new action potential is triggered.

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